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AF/1646

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TRANSMITTAL FORM

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Total Number of Pages in This Submission: 30

Application Number	10/005,438
Filing Date	December 3, 2001
First Named Inventor	Liming Yu, et al.
Art Unit	1646
Examiner Name	G. Chandra
Attorney Docket Number	95-02ABB (Case 0028 (05))

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☑ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Other Enclosure(s) (please Identify below):

See remarks.

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Tanox, Inc.		
Signature	Cheryl A Liljestrand		
Printed name	Cheryl A. Liljestrand		
Date	Sept 22, 2006	Reg. No.	45,275

CERTIFICATE OF TRANSMISSION/MAILING

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Signature	Cheryl A Liljestrand		
Typed or printed name	Cheryl A. Liljestrand	Date	Sept 22, 2006

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and1.14. This collection is estimated to 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PATENT
ATTORNEY DOCKET NO.: 95-02ABB
Customer No.: 26839

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Liming YU et al.

Serial No.: 10/005,438

Filed: December 3, 2001

For: HYBRID WITH INTERFERON-α AND AN IMMUNOGLOBULIN Fc FOR TREATMENT OF TUMORS

Group Art Unit: 1646

Examiner: G. Chandra

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

RESPONSE TO NOTICE OF NON-COMPLIANT APPEAL BRIEF

On August 31, 2006, the Office issued notification that the Appeal Brief filed on August 14, 2006 did not comply with the requirements of 37 CFR 41.37(c). This response is being filed within the one-month response period and therefore no fee should be due. However, should any fees be necessary, please charge our deposit account 20-0087.

Appellants have made the following corrections and submit the attached Appeal Brief in response to this Notice:

1) Exhibit A has been relabeled Section VIII; Exhibit C has been relabeled Section IX; and Section X was added (none).
2) Section III was amended to make it clear that claims 14-16 and 18-19 are being appealed.
3) Section V was amended to remove the reference to withdrawn claims.
4) Section VI was amended to make it clear that there is only one ground of rejection on appeal. In view of this amendment, Section VII should comply with the requirement that each ground of rejection be under its own heading.

5) Claim Appendix was amended to remove the listing of cancelled and withdrawn claims.

Appellants submit that the attached Appeal Brief complies with all of the requirements under 37 CFR 41.37(c).

Respectfully Submitted,

Dated: September 22, 2006.

BY: Cheryl A. Liljestrand

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Tel.: (713) 578-4182

PATENT
ATTORNEY DOCKET NO.: 95-02ABB
Customer No.: 26839

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Liming YU et al.

Serial No.: 10/005,438

Filed: December 3, 2001

For: HYBRID WITH INTERFERON-α AND AN IMMUNOGLOBULIN Fc FOR TREATMENT OF TUMORS

Group Art Unit: 1646

Examiner: G. Chandra

APPEAL BRIEF

I. Real Party in Interest

The subject application is owned by Tanox, Inc. of Houston, Tx.

II. Related Appeals and Interferences

There are no other appeals or interferences related to the subject application.

III. Status of the Claims

On May 12, 2006, appellant appealed from the final rejection of claims 14-16, 18 and 19, claims 1-13 having been cancelled, and claims 17, 20-22 having been withdrawn from consideration pursuant to a restriction requirement.

Claims 14-16 and 18-19 are currently being appealed.

IV. Status of Amendments

The appellant filed an amendment March 14, 2006. In the Advisory Action dated April 19, 2006, the Examiner indicated that the amendment was entered.

V. Summary of Claimed Subject Matter

Appellant's invention relates to interferon ("IFN") hybrid molecules comprising an interferon molecule joined at one end to one chain of an immunoglobulin "Fc" fragment without any linker between the IFN and Fc portions, and functional IFN-Fc variants

having at least 95% identity to SEQ ID NO 1 (representing the nucleotide and amino acid sequence of an IFN-α-Fc hybrid, with no linker). The IFN-Fc hybrids have a much longer half-life *in vivo* than the native interferon molecule. The IFN hybrids can be either interferon-alpha-Fc or interferon-beta-Fc hybrids. The preferred Fc fragment is a human IgG4 fragment.

Appellant's claimed invention of interferon-Fc hybrid molecules without any linker and functional variants thereof is described at page 1, paragraphs [0007], [0008], and [0010] of the published application US2003/0026779 (attached for convenience). Data supporting the extended half-life of the claimed hybrid molecules is presented in Example 1, page 2.

VI. Grounds for Rejection to be Reviewed on Appeal

Claims 14-16 and 18-19 have been rejected under 35 U.S.C. §103(a) as unpatentable over Landolphi (U.S. Pat. No. 5,349,053), in view of Frincke (EP 467,416) and Peterhans (Analytical Biochem).

VII. Arguments in Support of Patentability Over the 35 U.S.C. §103(a) Rejection

Claims 14-16, 18 and 19, stand or fall together. Claims 14-16, 18 and 19 have been rejected as unpatentable over Landolphi (U.S. Pat. No. 5,349,053), in view of Frincke (EP 467,416) and Peterhans (Analytical Biochem).

Appellants presented four arguments during the course of prosecution: (1) that Landolphi is not valid prior art because it does not provide an enabling disclosure for the teachings it is cited for; (2) there is no motivation to combine the references in the absence of Appellant's specification; (3) there is no reasonable expectation of success; and (4) unexpected results.

A. The Office's Statements in support of Rejection

The Office contends that "Landolphi teaches 'chimeric molecules that comprise a portion of a ligand molecule linked to the constant region of an immunoglobulins molecule' (column4, lines 10-13) wherein the Fc region is a human gamma heavy chain (column 6, lines 51-59." (Office Action dated April 25, 2005, page 12, first full paragraph.) The Office admits that the reference does not specifically teach interferon as the ligand, but states that Landolphi "contemplates lymphokines, the group of gene

(sic) which is well known to one of ordinary skill in the art that interferon belongs to." (Id. At page 12).

The Office then contends that "Frinke et al teach that interferon-α-antibody complexes make the IFNα more stable and desirable for in vivo use". (Id. At page 12, second paragraph). The Office admits that neither Landolphi nor Frinke teach a hybrid without a linker.

The Office then cites Peterhans for the teaching of an interferonaplha2/beta galactosidase hybrid molecule wherein beta galactosidase is fused to the C-terminus of interferon alpha2 as establishing the making of a functional hybrid molecule.

The Office concludes that "it would have been prima facie obvious to one of ordinary skill in the art to substitute the interferon/Fc gamma chain fragment molecule of Landolphi with interferon α of Frincke to make a hybrid molecule that would be stable for in vivo use because of the recognized stability of hybrid as a preferred use as set forth by Francke (sic). One of ordinary skill of the art would have been motivated to make a hybrid IFN-Fc without linker because it is easier to make a direct fusion of proteins as taught by Peterhans et al." (Office Action at page 12-13).

B. Appellant's Argument that Landolphi is Non-Enabling Prior Art

Before a reference can even be considered to constitute legally cognizable prior art, it must teach how to make what it discloses. *In re Hoeksema*, 399 F.2d 269, 274, 158 U.S.P.Q. 596, 600-01 (C.C.P.A. 1968) held that the "true test of any prior art relied on to show or suggest that a chemical compound is old, is whether the prior art is such as to place the disclosed 'compound' in the *possession of the public*" (emphasis added). The test whether a particular compound described in the prior art may be relied upon to show obviousness is whether the prior art provided an enabling disclosure with respect to the disclosed compound. *Ashland Oil, Inc. v. Delta Resins Refractones* 776 F2d. 281, 227 USPQ 657 (Fed. Cir. 1985). Because the evidence in *Ashland* showed that a certain compound was a "hypothetical structure", the court found it was not persuasive of obviousness.

In this case, the Office has admitted that Landolphi does not disclose interferon. The Landolphi patent merely lists lymphokines as possible ligands, with no specific

reference to interferons, thus these are merely hypothetical structures with no enabling disclosure. As further evidence of the fact that the Landolphi patent does not enable embodiments other that IL-2, exerpts from the prosecution history of the Landolphi patent were presented to the Examiner in the Response filed on April 25, 2005. These exerpts are provided for the Appeal Bd.'s convenience in Exhibit C. In the prosecution history of the Landolphi patent, the Examiner stated at page 5 of the Office Action dated March 23, 1992, (See Exhibit C):

> [P]age 7 merely list[s] several lymphokines and growth factors that can be used as the ligand. . . . . [T]he specification is non-enabling for the preparation of immunoligands broadly, nor is it evident that the scope of these immunoligand[s] would have a utility and possess the desired physical and functional properties for each portion of the immunoligand. Lymphokine (LK) is generic, and represent[s] a broad and diverse group of proteins that are functionally and patentably distinct, such that **the preparation of an immunoligand with one LK such as IL-2 cannot effectively predict or enable the preparation and usefulness of the entire scope of LK**. (emphasis added)

Applicants of the Landolphi patent were unable to rebut this rejection and ultimately had to narrow their claims to the immunoligand IL-2. (See Exhibits C). Thus, the Landolphi patent fails to provide the necessary teachings to put the public in possession of the full scope of the invention as disclosed and as such cannot constitute legally cognizable prior art for the presently claimed invention.

The Examiner never addressed this argument.

C. Appellant's Argument for Lack of Motivation to Combine References

Appellants contend that the Office has failed to meet its burden for establishing its *prima facie* case of obviousness on the grounds that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. See *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). In the present case, there is no suggestion or incentive to combine the references cited by the Office, and there is no reasonable expectation of success.

The Federal Circuit has repeatedly warned that the requisite motivation must come from the prior art, not applicant's specification. See *In re Dow Chem. Co. v. American Cyanamid Co.*, 837 F.2d at 473, 5 U.S.P.Q.2d at 1531-1532 ("[t]here must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure"). Using an applicant's disclosure as a blueprint to reconstruct the claimed invention from isolated pieces of the prior art contravenes the statutory mandate of § 103 of judging obviousness at the point in time when the invention was made. See *Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907, 5 U.S.P.Q.2d 1788, 1792 (Fed. Cir. 1988). Moreover, where the prior art has not recognized the "result-effective" capability of a particular invention parameter, no expectation would exist that optimizing the parameter would successfully yield the desired improvement.

Here, the Office has pieced together disparate references using the Applicants' specification as a guide. Landolphi discloses chimeric molecules that "exhibit the high degree of specificity associated with the ligand yet retain various effector functions characteristic of immunoglobulin heavy chains." (Abstract) These effector functions include fixing complement and/or mediating antibody dependent complement fixation. (Col. 2, lines 50-53.) The problem to be solved by Landolphi was "the need for increasing the specificity and improving binding affinity of immunoglobulins beyond the immunoglobulin gene superfamily, while retaining their useful characterisitics." (Col. 2, lines 30-33.) The purpose was not related to increasing the serum half-life of the hybrid

molecule. The IL-2 construct and experiments disclosed further that end. Therefore, the motivation to combine the Landolphi reference with the Frinke reference is not present.

Moreover, the Frinke reference does not teach fusion proteins. Frinke teaches creating antigen-antibody complexes between a given protein and an antibody that binds to that protein. This is a totally different mechanism of extending half-life and does not provide a motivation to combine this reference with Landolphi in the absence of Appellant's specification. Even assuming that this reference was considered, the attachment of the antibody to the antigen protein is through its **Variable** region, not the Fc constant region. There is no suggestion that using the construct of Landolfi would accomplish the same thing as the Ag-Ab complex taught by the '416 patent because they are two different approaches.

Peterhans goes even further afield because he was making β-galactosidase fusions for ELISA assays, which have nothing to do with *in vivo* half-life. A detection enzyme fused to a protein to aid in detecting bound proteins would not in any way suggest to the skilled artisan that one could improve half-life by such fusion. Moreover, the Office concludes that this serves as evidence for a functional hybrid molecule. However, ELISA assays do not establish that a molecule is functional, only that it can be bound to the plate through the attached molecule on the plate.

Thus, in view of the lack of suggestion or motivation to combine these references, absent the Applicants' specification, the Office has failed to establish a *prima facie* case of obviousness.

D. Appellant's Argument for Lack of Reasonable Expectation of Success

Appellants contend that the Office has failed to meet its burden for establishing its *prima facie* case of obviousness on the grounds that the proposed modification of the prior art lacks a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

The Office has also failed to establish a reasonable expectation of success. In moving from the prior art to the claimed invention, one cannot base a determination of

obviousness on what the skilled person might try or find obvious ***to try***. Rather, the proper test requires determining what the prior art would have led the skilled person ***to do***.

The Landolphi patent disclosure does not provide a reasonable expectation of success because it is a non-enabling disclosure and from statements made by the Examiner in the Landolphi patent prosecution. As pointed out by that Examiner (See excerpt text at page 4, above), there is no evidence that creating a hybrid molecule comprising an interferon-α molecule joined to an Fc fragment would "possess the desired physical and functional properties" based on the disclosure of the Landolphi specification. Thus, there is no reasonable expectation of success in making the presently claimed invention in view of the nonenabling disclosure of the Landolphi patent.

The EP467416 fails to overcome the deficiencies in the Landolphi patent. This specification discloses antibody compositions made by creating an antibody ("Ab") directed against the therapeutic agent, e.g., alpha-interferon, such that when the Ab binds to the therapeutic agent, it forms an antibody-interferon complex that does not impair the activity of the agent. However, this does not teach constructing a hybrid molecule wherein the alpha-interferon is joined to the immunoglobulin Fc fragment. Indeed, not only is the composition taught by EP467416 not a hybrid molecule, the Ab composition disclosed binds to the alpha-interferon through its **variable** region, not the constant region.

Peterhans also does not solve the deficiencies of the Landolphi patent. It merely discloses making β-galactosidase fusions for ELISA assays. This is clearly not a immunoglobulin Fc fragment hybrid molecule and thus, it does not suggest a hybrid interferon-Ig molecule nor does it provide a reasonable expectation of success.

Thus, the Office has not met its burden of establishing a *prima facie* case of obviousness for this additional reason. There is no reasonable expectation of success given the nonenabling teachings of the cited prior art.

E. Evidence Cited in Support of Unexpected Results

Appellants also presented evidence of un-expected results in the Response filed on March 14, 2006, which was improperly considered by the Office.

Appellants cited to the specification at Example 1, paragraph [0025] (Exhibit B) as further evidence of nonobviousness. The *in vivo* pharmokinetic studies in primates resulted in a 40-fold longer serum half-life than unmodified interferon. The clearance half-life after subcutaneous injection was almost 120 fold longer.

The Frinke reference (EP467416) only reported a 12-fold increase in half-life (col. 6, lines 53-57.) Since the Landolphi patent only constructed IL-2-Ig complexes, and does not disclose any increases in half-life because that was not the intended purpose of the Landolphi invention, the present invention clearly demonstrates unexpected results over this patent as well. Peterhans discloses labeled constructs for an entirely different purpose, thus no disclosure of increased half-life.

Clearly, a 40-fold increase in serum half-life of the claimed interferon-Fc hybrid molecule over interferon alone and a 120-fold longer clearance half-life is unexpected over the teachings of Frinke of 12-fold.

F. Summary

For the foregoing reasons, Appellant believes that the Office's rejection of claims 14-16 and 18-19 were erroneous, and reversal of her decision is respectfully requested.

Respectfully Submitted

By: Cheryl A. Lillestrand

Cheryl A. Lillestrand
Reg. No. 45,275

Dated: September 22, 2006

VIII. Claims Appendix

Claims on Appeal:

14. An IFN-Fc hybrid molecule comprising an interferon molecule joined at one end to one chain of an immunoglobulin Fc fragment without any linker between the interferon and the immunoglobulin Fc fragment, and functional IFN-Fc variants having at least 95% identity to SEQ ID NO 1.

15. The hybrid molecule of claim 14, wherein the interferon is interferon-α and is joined at its C-terminal end to the N-terminal end of the immunoglobulin Fc fragment.

16. The hybrid molecule of claim 14, wherein the Fc fragment is a gamma-4 chain Fc fragment, and wherein said fragment does not induce antibody-dependent cellular cytotoxicity (ADCC) or activate complement.

18. The hybrid molecule of claim 14, wherein the interferon molecule is interferon-α2a or interferon-α2b.

19. A composition comprising the hybrid molecules of any of claims 14 to 18 for treatment of tumors.

IX. Evidence Appendix

The attached evidence includes portions of the prosecution history for the Landolphi Patent cited in the grounds for rejection (U.S. Pat. No. 5,349,053). These portions of the prosecution history of the '053 patent were filed with the Response submitted on August 24, 2005, in response to the Non-Final Office Action dated April 25, 2005, and were entered on August 25, 2005.

X. Related Proceedings Appendix

NONE

Exhibit 1

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

07/532,267 06/01/90 LANDOLFI

ATTORNEY DOCKET NO.
N 11823-18

EXAMINER
DRAPER, G

TOWNSEND & TOWNSEND
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ONE MARKET PLAZA
SAN FRANCISCO, CA 94105

ART UNIT	PAPER NUMBER
1812	8

DATE MAILED: 03/23/92

Commissioner of Patents and Trademarks

☒ This application has been examined ☒ Responsive to communication filed on 1-17-92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-24 are pending in the application.
   Of the above, claims 16-22 and 24 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-15 and 23 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

1. The Examiner gratefully appreciates applicant's compliance with their Duty of Disclosure, the Disclosure Statement, the cited art, and the completed PTO 1449.

2. First of all it is pointed out that through an inadvertent oversight the examiner's restriction appears to have suggested that claims 1-15 and 23 were directed to immunoligands between the Ig constant region and IL-2; however, claim 11-14 are not restricted to IL-2, but instead encompass immunoligands wherein the ligand are broadly growth-factor like moieties, or presumably, broadly lymphokine-like moiety. In view of such, an election of specie would have been proper; however, no further election will be required at this time.

Applicant's election with traverse of Group I, claims 1-15 and 23 in Paper No. 7 of 1-17-92 is acknowledged. The traversal is on the ground(s) that the groups are so closely related that they should remain in the same application, because they related to immunoligands wherein the ligand is linked to the Ig constant region. This is not found persuasive because relatedness is not a sufficient basis to assume that a restriction should not be made therebetween, particulary when the Examiner has set forth sufficient reason for requiring this restriction. Applicant has not sufficiently establish that the restriction is in error. The requirement is still deemed proper and is therefore made FINAL.

4. The title of the invention is not descriptive. A new title

is required that is clearly indicative of the invention to which the claims are directed.

The following modification to the title is suggested since immunoglobulins per se are not being claimed. Instead of "/Immunoglobulin" it is suggested that "/Immunoligand" be substituted-provided that by the designation "Chimeric Ligand/Immunoglobulin" applicant is using the "/" to designate an alternative name for the protein. If the latter is not the case, then an amendment or clarification of the title is request.

5. First of all it is pointed out that there has been several case law decisions that have held that rejection sunder 35 USC 101 for operative utility, and 35 USC 112 first paragraph for sufficient enablement are often appropriately coupled and judicially accepted; and that such rejections can be combined because there is typically one issue (See In re Gardner, 117 USPQ 396; In re Fouche, 169 USPQ 429; and Ex parte Stevens, 16 USPQ 2d. 1379).

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

The following is a quotation of the first paragraph of 35 USC §112:

The specification shall contain a written description of the

invention, and of the manner and process of making and using it, in such full clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best made contemplated by the inventor of carrying out his invention.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure; and because the invention as disclosed and claimed in inoperative and non-enabling, and therefore lacks patentable utility.

First of all applicant's invention appears to rely on the use ~~would~~ of novel cell lines that produce chimeric molecules/immunoligands wherein the immunoligands require specific portions of immunoglobulins (Ig) that possess specific regions that possess required functional properties. In view of such unique properties, the reproduction of such, in the absence of a deposit, would require undue experimentation to reproduce such altered Ig (immunoligands) that possess the desired physical

and functional properties. Therefore, it is suggested that applicants comply with all of the provisions of MPEP 608.01 (p)(c) regarding deposit of biological material. Assurance of compliance may be an the form of a Declaration or averment under oath.

Secondly, at page 4 general reference is made to growth-factor like moiety; and page 7 merely list several lymphokines and growth factor that can be used as the ligand. However, only one immunoligand was prepared wherein IL-2 was the ligand while this specific immunoligand has a disclosed utility, the specification ~~is non-enabling~~ is non-enabling for the preparation of immunoligands broadly, nor is it evident that the scope of these immunoligand would have a utility and possess the desired physical and functional properties for each portion of the immunoligand. Lymphokine (LK) is generic, and represent a broad and diverse group of proteins that are functionally and patentably distinct, such that the preparation of an immunoligand with one LK such as IL-2 can not effectively predict or enable the preparation and usefulness of the entire scope of LK. Since the corresponding receptors for these LK have different structural motifs, the interaction of a LK to its corresponding receptor differs as well as the signal transducing properties. Therefore, the presence of an Ig portion conjugated to the LK may present a problem for the ligand (L) to receptor interaction.

Antagonist and lymphokine inhibitors are also different from the L per se. Furthermore, applicant's specification fails to provide sufficient guidance in the absence of a sufficient number of enabling examples that cover the scope of the ligands.

Furthermore, the scope and intent of growth factor-like ligand has not been clearly define. "Like" in what respect and degree. In view of the specifics that were disclosed for the particular IL-2/IgG1, it would appear that specific portion of the IL-2 and IgG1 are necessary for the preparation of functionally active immunoligand that possess the desire activity (See pgs 5, and 18-20 of the specification)

Claims 1-15 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-15 and 23 relative to the deposit issue are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

And claims 1-7, 11-14 and 23 are rejected under USC 101 because the disclosed and claimed invention is inoperative and therefore lacks demonstrated and patentable utility; and the claim are rejected under 35 USC 112, first paragraph, for the reasons set forth in the objection to the specification.

6. Claims 1-15 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person

skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7, and 23 are broad and indefinite with regard the scope and intent of "ligand component", because this term does not make clear that all or a portion of the ligand is contemplated; or if the two words are used to collectively describe one part of the immunoloigand. In a similar manner, claims 1, 5-7 and 23 are broad, indefinite and confusing in the use of "constant region component".

Claims 11-14 and 23 are broad, indefinite and confusing in the use of "growth-factor-like". Like in what respect? These claims are also broad and indefinite in the use of "moiety".

7. Claims 4, and 12-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is indefinite in the use of improper Markush language according to MPEP 706.03(Y); therefore, it is suggested that the claim be amended as follow: "...component selected from the group consisting of a hinge region...."

Claim 12 is indefinite and incomplete because there is no antecedent basis in claim 11 for "the ligand component" per se because independent claim 11 specifically refers to a "growth

factor-like moiety.

Claim 13 is indefinite, contradictory and fails to have antecedent basis in the earlier portion of the claim for "the growth-factor-like moiety", because the claim initially referred to a "lymphokine like moiety". These two terms are not exactly the same.

Claim 14 is indefinite and does not have antecedent basis in claim 12 for "the heavy chain constant region..."

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this

section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-2, 6-7 are rejected under 35 U.S.C. § 102(a or b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Traunechker et al or Schnee et al or von Wussow

Applicants claims are directed to immunoligands wherein an Ig constant region is linked to the ligand. Although not referred to as immunoligands, the prior art disclose Ig fused to a protein such as TPA, interferon or Interleukin 1c from von Wussow), and the CD4 antigen that are considered ligands within the meaning of the claims (See the abstract of each).

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

The other art listed on the PTO 892 is cited as of interest.

10. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1812.

11. Any inquiry concerning this communication should be directed to Exm. G. D. Draper at telephone number (703) 308-0196.

Draper/tf
February 26, 1992

Garnette D. Draper
GARNETTE D. DRAPER
PRIMARY EXAMINER
ART UNIT ~~185~~ 1812

EXHIBIT C

#11/a
m.b.
11/10/92

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on 23 September 1992

BY Tracy J. Dunn

PATENT

Attorney Docket No. 11823-18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	
NICHOLAS F. LANDOLFI	Examiner: DRAPER
Serial No.: 07/532,267	Art Unit: 1812
Filed: 1 June 1990	AMENDMENT
For: CHIMERIC LIGAND/IMMUNOGLOBULIN MOLECULES AND THEIR USES	

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

In response to the Office Action dated 23 March 1992, Applicants respectfully request reconsideration and reexamination of the claims of the above-identified application in view of the following amendments and remarks.

AMENDMENTS

IN THE TITLE

Please delete the title and replace therefor the following replacement title:

--Immunoligands Comprising An Immuoglobulin Constant Region Component and a IL-2 Receptor Binding Component--

IN THE SPECIFICATION

On page 4, line 2, delete "growth factor-like moiety" and substitute therefor --growth factor amino acid sequence--.

IN THE CLAIMS

1.(amended) An immunoligand comprising a ligand component linked in peptide linkage to an immunoglobulin constant region component comprising an immunoglobulin domain, and wherein

the ligand component comprises an amino acid sequence of interleukin-2 capable of binding an interleukin-2 receptor and the immunoligand is capable of binding to a cell surface receptor through the ligand component.

5.(amended) An immunoligand of claim 1, wherein the ligand component is linked to the constant region component via a peptide bond to a hinge region of said constant region component.

9.(~~amended~~) An immunoligand of claim 8 wherein the ligand component comprises [an amino acid sequence of interleukin-2 capable of binding an] a human interleukin-2 [receptor] protein.

11.(amended) An immunoligand comprising a growth factor amino acid sequence [-like moiety] linked in peptide linkage to at least one domain of an immunoglobulin heavy chain constant region, wherein the growth factor amino acid sequence [-like moiety] is capable of binding to a cell surface receptor.

12.(amended) An immunoligand of claim 11 wherein the [ligand component] growth factor amino acid sequence is [linked to the constant region component by a peptide bond] a naturally-occurring peptide or protein molecule.

13.(amended) An immunoligand of claim 12 comprising [a lymphokine-like moiety] an interleukin-2 amino acid sequence linked in peptide linkage to at least one domain of an immunoglobulin heavy chain constant region wherein the [growth factor-like moiety] immunoligand is capable of binding to a cell surface interleukin-2 receptor.

14.(amended) An immunoligand of claim 12 wherein the heavy chain constant region is a human IgG1 heavy chain constant region.

23.(amended) A pharmaceutical composition comprising a suitable carrier and an immunoligand of claims 1 or 12, wherein the immunoligand binds to an interleukin-2 receptor.

Amended claims 1, 5, 9, 11-14, and 23, and original claims 2-4, 6-8, 10, and 15 are pending. Applicant respectfully requests that the Examiner enter the amended claims.

REMARKS

Before addressing the rejections raised by the Examiner, it is appropriate to briefly discuss the claimed invention. The invention as now claimed comprises immunoligands, which are chimeric proteins comprising a polypeptide hormone or growth factor sequence that binds to a cell surface receptor linked, in peptide linkage, to an immunoglobulin constant region component comprising an immunoglobulin constant region domain. As now claimed, the invention relates to immunoligands which bind to the inteleukin-2 (IL-2) receptor, which are not described and enabled by the cited references.

Objection to the Title and Specification

The Examiner has objected to the title as being insufficiently descriptive. Applicant has amended the title to more closely describe the claimed invention.

The Examiner has also objected to the Specification under 35 U.S.C. §112, first paragraph as being a description of an invention which is inoperative, non-enabling, and lacking patentable utility. The Examiner has requested a deposit of a cell producing the exemplified embodiment. The Applicant believes that the example provided in the Specification, beginning on page 18, line 10 and continuing to the end of the Specification is sufficiently detailed, indeed more than sufficiently detailed, to permit one of skill in the art to practice the invention. Each component listed in the Specification on page 18, beginning on line 19, is readily available to those of skill in the art in polynucleotide form, or as a GenBank or other published polynucleotide sequence which can be readily interconverted into polynucleotide form by making (and ligating if necessary) synthetic oligonucleotides on the basis of the sequence data. Given these components, the construction of vectors, transfection, purification of the immunoligand, and its usage is described in more than sufficient detail to permit those of skill in the art to prepare and purify an immunoligand that binds to the IL-2 receptor. Therefore, the Specification describes the invention in sufficient detail to be enabling, and

the exemplified embodiment is shown, in the Specification to be operative in producing the immunoligand. The Examiner's requirement for deposit is respectfully traversed, as the invention is fully enabled by the detailed description of the exemplified embodiment.

As to the Examiner's contention that the invention lacks patentable utility, Applicant directs the Examiner's attention to the following excerpts from the Specification as proof of patentable utility:

On page 23, lines 22-29:

> The chimeric molecule was capable of stimulating proliferation of the CTLL cell line, and comparison with the proliferation stimulated by recombinant human IL-2 revealed that on a per molecule basis, the chimeric IL-2/IgG1 has a specific activity indistinguishable from recombinant human IL-2 (Fig. 4a). Thus, the IL-2 moiety of the chimeric molecule is in a fully functional configuration, exhibiting both the binding and proliferation-mediating activities of IL-2.

On page 23, lines 35-37:

> IL-2/IgG1 was compared with the murine anti-Tac monoclonal antibody for the ability to mediate complement-dependent lysis of the HuT-102B cell line.

On page 24, lines 14-16:

> IL-2/IgG1 has the ability to specifically lyse HUT-102B cells in the presence of complement, although at a somewhat less efficient level than does anti-Tac (Fig. 4b).

On page 24, lines 20-29:

> IL-2/IgG1 was also examined for the ability to mediate ADCC. The murine anti-Tac monoclonal does not mediate ADCC, however the chimeric and humanized versions of this antibody exhibit detectable levels of ADCC activity with the use of an activated effector cell population (Junghans, et al., supra. IL-2/IgG1 and chimeric anti-Tac each exhibited a small (28% and 15%, respectively) enhancement of lysis of HuT-102B target cells in a four hour assay. In conclusion, these results indicate that the IL-2/IgG1 molecule possesses the functional activities of both the IgG and IL-2 moieties.

Applicant believes that the demonstration of the efficacy of the immunoligand in the complement-dependent lysis assay and the ADCC assay demonstrates patentable utility. The Examiner is reminded of the recent Board decision in Ex Parte Aggarwal, 23 USPQ2d 1334 (BPAI, 1992), copy enclosed, wherein the Board staes, on p.1339:

> Case law subsequent to Brenner is receptive to early filing of applications in the biomedical field so long as the patent applicant, when properly challenged by the examiner, can provide evidence showing substantial activity in screening tests customarily used and accepted as predictive of human activity for the type of chemical tested. Of course, the evidence presented must be commensurate with the scope of utility asserted and the subject matter claimed.

Applicant submits that the complement-dependent lysis assay and the ADCC assay results using the IL-2 immunoligand are sufficiently predictive of its biological and immunological activities to indicate that the invention possesses patentable utility in accordance with Ex Parte Aggarwal. Applicant therefore requests that the Examiner withdraw the objection to the Specification as describing an invention that lacks patentable utility.

Rejection Under 35 U.S.C. §§101 and 112, First Paragraph

The Examiner has rejected Claims 1-15 under 35 U.S.C. §112, first paragraph as describing an invention that is non-operative, non-enabled, and lacking patentable utility for the reasons cited in the objection to the Specification. Claims 1-15 and 23 were rejected by the Examiner under 35 U.S.C. §§101 and 112, first paragraph, as being nonenabling without a deposit being made. For the reasons cited above, the detailed exemplification in the Specification and the assay results, and the amendments to the Claims, Applicant respectfully requests that the Examiner withdraw the rejection.

Rejection Under 35 U.S.C. §112, First and Second Paragraphs

The Examiner has rejected Claims 1-15 under §112, first and second paragraphs for being an allegedly non-enabling description and for failing to point out and distinctly claim the

invention. Claims 1-7 and 23 were rejected as broad and indefinite for use of the word "ligand component". Although the term "ligand component" is described in the Specification on page 3, lines 33-37, and described and exemplified with multiple examples on page 7, lines 7-32, Applicant has amended the Claims to clarify the term further. Claims 1, 5-7, and 23 were rejected as broad, indefinite, and confusing in the term "constant region component". The term "constant region component" is defined in the Specification, on page 6, lines 29-34, and the Claims have been amended to clarify the term further. Claims 11-14 and 23 were rejected as broad, indefinite, and confusing in the use of "growth factor-like" and "moiety". As amended, these claims no longer use the term "growth factor-like" or "moiety".

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected Claims 4 and 12-14 under §112, second paragraph as being indefinite. The Examiner rejected Claim 4 as reciting improper Markush language. Respectfully, Claim 4 is not a Markush claim, indeed it is more limited in that it recites that the constant region component consists of all of the elements: hinge region, C_H2 domain, and C_H3 domain. The rejection of Claim 12 and Claim 13 for the cited language has been addressed by amendement of the claims. Claim 14 has antecedant basis for "the heavy chain constant region" in that Claim 14 depends from dependent Claim 12 which draws antecedant basis for the term from Claim 11.

Rejections Under 35 U.S.C. §§102(a), 102(b), and 103

The Examiner has rejected Claims 1-2 and 6-7 under 35 U.S.C. §102 (a or b) or, in the alternative §103, in view of the cited Traunecker et al., Schnee et al., and von Wussow et al. The cited art is readily distinguished from the present invention as now claimed, and discussion of the cited art is not an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention.

Traunecker et al. describes making an immunoglobulin chain having a portion of the CD

C_H1 domains of γ2a or μ chains. The immunoglobulin chains made by Traunecker et al. bound a free viral glycoprotein, gp120, but were not reported to either: (1) bind to a cell surface receptor, such as an Il-2 receptor, or (2) to possess biological activity as defined by complement-mediated lysis, ADCC activity, or IL-2 activity. Therefore, Traunecker et al. neither anticipates nor makes obvious the claimed invention.

Schnee et al. reports a heavy chain-tPA fusion polypeptide having a fraction of the peptidolytic tPA activity of native tPA. The fusion protein reported by Schnee et al. did not: (1) bind to a cell surface receptor, such as an IL-2 receptor, (2) have demonstrated complement-mediated lysis, ADCC activity, or IL-2 cytokine activity. Therefore, Schnee et al. neither anticipates nor makes obvious the claimed invention.

Von Wussow et al. disclose making an immunoconjugate wherein a purified α-interferon molecule is linked to an immunoglobulin molecule by a non-peptide chemical linkage. The non-peptidyl linkage of two purified proteins differs from the claimed invention in several respects. First, the effector functions of the immunoglobulin in the von Wussow conjugate were not shown to be elicited (and would not be expected) by binding of α-interferon to its receptor, whereas Applicants IL-2 immunoligand has demonstrated effector functions upon binding (e.g., complement-mediated lysis). Second, von Wussow does not show that the α-interferon conjugate is able to target cells bearing a α-interferon receptor and mediate ADCC. Finally, the immunoconjugate of von Wussow does not indicate that one of skill in the art would have a reasonable expectation of success in making the IL-2 immunoligand of the Applicant's invention, which is biologically active as a cytokine and has ADCC and complement-mediate lysis activity, which are not predicted by von Wussow. Therefore, von Wussow et al. neither anticipates nor makes obvious the claimed invention.

Therefore, Applicant submits that the invention, as now claimed, is not anticipated under §102 (a or b) and is not obvious under §103.

Summary

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 326-2400.

Respectfully submitted,

TOWNSEND and TOWNSEND

By _____
Tracy J. Dunn
Reg. No. 34,587

TOWNSEND and TOWNSEND
One Market Plaza
Steuart Street Tower, 20th Floor
San Francisco, California 94105

(415) 326-2400

TJD:lkj

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Exhibit 3

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/532,267	06/01/90	LANDOLFI	N 11823-18

EXAMINER
DRAPER, G

ART UNIT	PAPER NUMBER
1812	13

DATE MAILED: 02/10/93

TOWNSEND & TOWNSEND
STEUART STREET TOWER
ONE MARKET PLAZA
SAN FRANCISCO, CA 94105

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 9-28-92 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-24 are pending in the application.
   Of the above, claims 16-22 and 24 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-15 and 23 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-24 are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

1. The following objections and rejections have been withdrawn.

-regarding a proper title.

-the 35 USC 112 for "growth like"

-portions of the 35 USC 101 aspect of the previous rejection, and only certain portions of the previous 35 USC 112/1st aspect of this rejection not herein restated

-the requirement for a deposit

-the alternative 35 USC 112 1st/2nd paragraph rejection.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Applicant's arguments filed 9-28-92 have been fully considered but they are not deemed to be persuasive.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure and for back of demonstrated utility.

Claims 11-12 and 14 are rejected under 35 USC 101 for lack of demonstrated utility, and these claims are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the

objection to the specification.

The objection and the rejections are maintained only with regard to these broad claims for the reasons set forth in the previous office action at pages 5-6. Most of applicants arguments were directed to the IL-2-Ig immunoligands; however, these claims are broadly directed to any growth factor -Ig immunoligand. The preparation of one such product is not predictive and enabling for the broad scope of growth factors and Ig fusions. The presence or absence of other growth factors on surface of various cells is not clear; nor whether the respective ligand-receptor interaction is present and readily associated with the desired condition to be treated; especially for cell-lytic activity or ADCC.

5. Claim 8 is rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claim 1, from which claim 8 depends, has been amended to recite IL-2 as the ligand therefore the claim is not further limiting.

6. Claims 11-12 and 14 are rejected under 35 U.S.C. § 102(a or b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Tranuechker et al or Schnee et al or von Wussow.

These rejections are maintained for the reasons set forth in

the previous office action. Applicant has merely stated the make-up of the immunoligands of the prior art, and has further argued their patentability relative to IL-2; however these claims are broadly directed to immunoligands and are not restricted to IL-2. Accordingly, they would not be expected to possess the same kind of activity as the IL-2--immunoligand. Applicant has not proffered evidence or sufficient arguments to support their position that the prior art immunoligands do no bind to the respective cell surface receptors, possess complement-medicated lysis, or ADCC. Therefore, this appears to represent unsupported allegations.

It is believed that tall pertinent arguments have been answered.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Claims 1-10, 13, 15 and 23 are rejected under 35 U.S.C. § 103 as being unpatentable over Von Wussow et al.

Even though the claims have been amended to limit them to the immunoligand comprising IL-2 as the ligand component, the claims are still prima facie obvious over the art because IL-2 is specifically taught as being usable in the immunoligand construct, therefore, one having ordinary skill in the art would have used the teachings therein to construct immunoligands with any one of the disclosed ligands. Since the prior art listing of IFN and

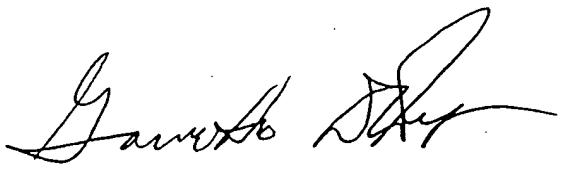
IL-2 implies that they would be functionally equivalent in such immunoligand, the skilled artisan would have reasonably expected that either of these cytokine ligands could be used in the immunoligand for similar functions. Contrary to applicants assertion, it has been well known in the art that IFN mediate ADCC and complement-mediated lysis. Furthermore, the resulting biological activity of the various immunoligands is not the controlling issue of obviousness, but rather, whether the prior art disclose the product per se or render it obvious. Herein the construction of IL-2 immunoligands are obvious from the art.

The prior art listed on the PTO-892 is cited as of interest to show related art.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Draper/tf
February 02, 1993



GARNETTE D. DRAPER
PRIMARY EXAMINER
ART UNIT 186

Corres. and Mail Exhibit 4

BOX AF

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Box AF, Washington, D.C. 20231, on May 10, 1993

By J Wehrschmetz

MAIL ROOM MAY 14 1993 PAT. & TM OFFICE

#141

AMENDMENT UNDER 37 CFR 1.116
EXPEDITED PROCEDURE -
EXAMINING GROUP 1812

PATENT

Attorney Docket No. 11823-18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

NICHOLAS F. LANDOLFI

Serial No.: 07/532,267

Filed: June 1, 1990

For: CHIMERIC LIGAND/ IMMUNOGLOBULIN MOLECULES AND THEIR USES

Examiner: G. Draper

AMENDMENT AFTER FINAL

ENTERED

RECEIVED
MAY 18 1993
GROUP 1800

Box AF
Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

In response to the Final Office Action mailed February 10, 1993 (Paper No. 13), please amend this application as follows:

IN THE CLAIMS:

Please cancel claims 1, 11, 12, 13 and 14 without prejudice to subsequent renewal.

Please amend the following claims as indicated:

2. (Amended) An immunoligand of claim [1] ~~25~~ wherein the constant region component is a heavy chain constant region.

5. ~~(Twice Amended)~~ An immunoligand of claim [1] ~~25~~, wherein the ligand component is linked to the constant region component via a peptide bond to a hinge region of said constant region component.

6. ~~(Amended)~~ An immunoligand of claim [1] ~~25~~ wherein the immunoligand is capable of fixing complement through the constant region component.

7. (~~Amended~~) An immunoligand of claim [1] ~~25~~ 1 wherein the immunoligand is capable of mediating antibody dependent cell cytotoxicity through the constant region component.

8. (~~Amended~~) An immunoligand of claim [1] ~~25~~ 1 wherein the ligand component is a naturally occurring interleukin-2.

~~11~~ 25. (Amended) An immunoligand [comprising interleukin-2 linked to a human IgG1 heavy chain constant region] of claim 3, wherein [the interleukin-2] the sequence comprises an additional C-terminal hydrophilic residue [and is capable of binding an interleukin-2 receptor].

~~12~~ 23. (Twice Amended) A pharmaceutical composition comprising a suitable carrier and an immunoligand of [claims 1 or 12] claim ~~25~~ 1, wherein the immunoligand binds to an interleukin-2 receptor.

PLEASE ADD THE FOLLOWING NEW CLAIM:

~~25~~. ~~An~~ A chimeric immunoligand comprising:

an interleukin-2 ligand component comprising an interleukin-2 amino acid sequence capable of binding an interleukin-2 receptor; and

an immunoglobulin constant region component comprising an immunoglobulin constant region domain without an immunoglobulin variable region domain;

wherein the ligand component and the constant region component are in peptide linkage, the immunoligand is capable of binding to an interleukin-2 cell surface receptor through the ligand component, and the immunoligand is capable of fixing complement and/or mediating antibody dependent cell cytotoxicity through the constant region component, due to binding of the immunoligand to the cell surface receptor.

REMARKS

Claims 2-10, 15, 23 and 25 are pending. Note that new claim 25 is based on cancelled claim 1 but differs in three respects. First, additional language has been added to clarify that the constant region component is lacking a variable domain. Support for this amendment is provided by the specification at

page 6, lines 7-9 and lines 31-34. The specification explains that the ligand component replaces all or substantially all of the immunoglobulin variable domain, and that the constant region component therefore usually contains ten or fewer amino acids from the variable region. Second, an additional limitation has been added specifying that the immunoligand is capable of mediating complement fixation or ADCC through the constant region component due to binding of the immunoligand to the cell surface receptor. Support for this amendment is provided throughout the specification, for example p. 8, lines 31-32 and pp. 23-24. Third, the format of claim 25 has been somewhat modified from that of claim 1 for ease of comprehension.

The Examiner has rejected claim 8 under 35 USC §112, fourth paragraph for failing to further limit the subject matter of a previous claim. In response, Applicant has amended claim 8 to clarify that it specifies an additional limitation over claim 1, namely that the ligand component is a naturally occurring IL-2 ligand. Support is provided at page 7, line 10 of the specification.

The only other outstanding rejection against the pending claims is that the Examiner has stated that they are obvious under 35 USC §103 over Von Wussow. All other rejections have become moot in view of the claim cancellations.

The Invention

The invention, as specified in claim 25, is directed to an immunoligand comprising an IL-2 ligand and a constant region of an immunoglobulin chain. The IL-2 ligand is peptide bonded to the constant region. The immunoligand is capable of binding to the IL-2 receptor through the IL-2 component and of fixing complement and/or mediating ADCC through the constant region component due to binding of the IL-2 component.

Von Wussow

Von Wussow discusses production of an INF-α complex by chemical crosslinking of purified INF-α ligand and an intact immunoglobulin to form a product that is not in peptide linkage.

Von Wussow also mentions that other ligands potentially be used in place of IFN-α, but does not exemplify these alternative chemically crosslinked complexes. Von Wussow reports that the INF-α/immunoglobulin complex has a longer serum half-life than free INF-α. Von Wussow does not describe any tests to establish whether his complex could mediate complement-dependent lysis or ADCC due to binding of the INF-α moiety to its receptor, nor does he recognize the utility of these properties in any fusion proteins.

Von Wussow distinguished

The Examiner states that von Wussow specifically teaches IL-2 and INF as functional equivalents in this context. The Examiner states that contrary to Applicant's prior arguments, it is well known in the art that IFN mediates ADCC and complement-mediated lysis. The Examiner also notes that the biological activity of the various immunoligands is not the controlling issue of obviousness. Applicant respectfully traverses this rejection.

Von Wussow does not disclose at least two important structural features of the claimed IL-2 immunoligands. In the claimed immunoligands, the ligand portion is attached to the constant region of an immunoglobulin chain (thereby replacing substantially all of the immunoglobulin's natural variable region) by a peptide bond. By contrast, in Von Wussow's complex, the ligand portion is attached to an intact immunoglobulin, at a presumably random location, by chemical cross-linking. Applicant agrees with the Examiner that Von Wussow mentions, albeit prophetically, that an immunoglobulin complex might also be constructed from an IL-2 ligand in place of the INF-α ligand exemplified. However, patentability over Von Wussow is not premised merely on the difference between IL-2 and INF-α, but rather on the difference between an immunoglobulin chain constant region and an intact immunoglobulin, and the difference between a peptide linkage and a chemical cross-linkage. These structural differences from the claimed immunoligands exist irrespective of the particular ligand used in Von Wussow's complex.

The claimed immunoligands exhibit several advantages that the complexes discussed by Von Wussow have not been shown to possess. These advantages are relevant to patentability in that acquisition of advantageous functional properties substantiates the nonobviousness of underlying structural modifications. A major advantage of the claimed immunoligands is that they confer the IL-2 cell surface receptor binding-specificity of the IL-2 ligand moiety, and the effector functions of the immunoglobulin constant region moiety responsive to binding of the IL-2 ligand moiety to its receptor. Thus, the claimed immunoligands are functionally very similar to natural immunoglobulins, but with the added advantage that binding specificity and affinity is predetermined by choice of the IL-2 ligand. By contrast, Von Wussow's complex, which retains the immunoglobulin moiety variable region, will bind either to an antigen recognized by the ligand moiety and to an unrelated antigen recognized by the immunoglobulin moiety. Moreover, Von Wussow provides no indication that the immunoglobulin moiety of his complex has capacity to mediate effector functions responsive to binding of the ligand moiety. Nor would such capacity appear particularly likely to exist in view of the unnatural chemical cross-linkage between the ligand and immunoglobulin moieties. Presumably, this unnatural linkage lacks the capacity to transduce conformational changes that occur on ligand binding, and which may be important for effector function such as ADCC and complement fixation.

The Examiner's observation that it is well known that INF stimulates ADCC does not imply that Von Wussow's INF-α-complex exhibits effector functions analogously to the claimed IL-2 immunoligands. IFN-α effects a generalized (i.e. nonantigen-specific stimulation) of ADCC via macrophage activation. See Paul, Fundamental Immunology (2d ed. 1989) at p.649. Thus, it is likely that the INF-α moiety of Von Wussow's complex acts in the same manner as free INF-α to effect a generalized stimulation of ADCC activity on binding of the immunoligand to macrophages. However, this stimulation would be a result of the IFN-α ligand possessing INF-α activity, not as a result of its conjugation to an immunoglobulin. This INF-α-

mediated generalized stimulation is entirely different from complement-dependent cytolytic activity or ADCC effected by the claimed IL-2 immunoligands. Here, binding of the IL-2-immunoligand to its receptor induces binding of complement and/or cytolytic cells specifically to the IL-2-immunoligand and not a generalized stimulation of cytolytic activity toward any bound antibody. Accordingly, the claimed IL-2 immunoligands can be used to eliminate a specific class of cells bearing their receptor, an advantage not conferred by generalized INF-α stimulation of ADCC activity. Moreover, if the INF-α of Von Wussow's complex were substituted with an IL-2 ligand, the new complex would not of course even be capable of inducing generalized stimulation of ADCC via the INF-α ligand.

Further advantages conferred by the claimed immunoligands over Von Wussow's complex are ease of production and reproducibility of therapeutic application. The claimed immunoligands can be produced as homogenous polypeptides of predetermined structure from a single recombinant DNA expression system. By contrast, preparation of Von Wussow's complex requires separate purification of ligand and immunoglobulin, a chemical cross-linking reaction, and purification of cross-linked product. Moreover, chemical cross-linking usually gives rise to a heterogenous mixture of products, which can lead to irreproducible results in use of the complex.

Not only does Von Wussow fail to disclose the important structural features noted above, he provides no suggestion to modify his complex to achieve the claimed invention. Von Wussow indicates that the purpose of linking INF-α to an immunoglobulin was merely to increase the half-life of circulating INF-α. Von Wussow fails to recognize the advantages of combining a ligand of known binding specificity with the effector functions of an immunoglobulin (in contrast to attempting to select a natural immunoglobulin having the same binding characteristics as the ligand). Absent disclosure of this advantage of the claimed immunoligands, one of ordinary skill would lack motivation to attempt to produce them.

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The nonobviousness of the claimed immunoligands is further substantiated by their unexpected properties. The combination of an IL-2 ligand with an immunoglobulin constant region into a single contiguous peptide molecule places conformational constraints on the respective components, which would have had an unpredictable effect on their respective functions (e.g., binding to the IL-2 receptor, complement fixation and ADCC activity). Surprisingly, it has been found that the claimed immunoligands exhibit functional properties of both components, namely capacity of IL-2 ligand to bind to its receptor and capacity of the immunoglobulin constant region to effect complement-dependent cell lysis. Still more surprisingly, the immunoglobulin constant region component also exhibits ADCC activity, which is not shown by the native murine immunoglobulin from which the constant region component was derived. These surprising results are entirely unpredictable from Von Wussow's work. In Von Wussow's complex, the ligand and immunoglobulin components are in a different physical linkage and therefore under different conformational constraints than the components of the claimed immunoglobulins. Moreover, as noted above, Von Wussow provides no indication that his complex has capacity for complement-dependent cytotoxicity or ADCC, much less that the claimed immunoligands would have these properties.

For all the above reasons, Applicants respectfully submit that the rejection of the claimed IL-2-immunoligands over Von Wussow should be withdrawn.

In light of the amendments to the claims, the application is in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at (415) 326-2400.

Respectfully submitted,

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Exhibit 5

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/532,267	06/01/90	LANDOLFI	N 11823-18

18M1

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EXAMINER	
DRAPER, G.	
ART UNIT	PAPER NUMBER
1812	15

DATE MAILED: 05/28/93

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☒ THE PERIOD FOR RESPONSE:

a) ☐ is extended to run _____ or continues to run _____ from the date of the final rejection

b) ☒ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition , and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☒ Applicant's response to the final rejection, filed 5-14-93 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☐ The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:

   a. ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.

   b. ☐ They raise new issues that would require further consideration and/or search. (See Note).

   c. ☐ They raise the issue of new matter. (See Note).

   d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

   e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☒ Upon the filing an appeal, the proposed amendment ☒ will be entered ☐ will not be entered and the status of the claims will be as follows:

   Claims allowed: 0
   Claims objected to: 0
   Claims rejected: 25, 2-10, 15, 23 Note. The 35 USC 103 rejection over Von Wussow is the only rejection remaining.

   However;

   ☒ Applicant's response has overcome the following rejection(s): combined 35 USC 101/112 1st paragraph over canceled claims 11-12, 14, as well as the different 103 rejection; the 112/4th paragraph.

4. ☐ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because No evidence has been presented for an advantage of claimed product relative to the use of constant region vs intact Ig, for a peptide linked from a fusion vs chemical cross-link; or that these are advantages in ADCC as Complent lysis is (below)

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficent reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☒ Other As a result of manner in which final product is made or linked. Since both IDN and II-2 are known to mediate the above activities, as well as Ab/Ig, one would reasonably expect that fusions or complexes containing such would also possess these activities. No evidence also shows that prior arts complex does not contain a peptide link. Further, above activities are known to be mediated by receptors.

GARNETTE D. DRAPER
PRIMARY EXAMINER
ART UNIT 185

PTOL-303 (REV. 5-89)